

Strengthening the PREP Stakeholder Dialogue: Researcher and Community Update

Report of a meeting convened by the International AIDS Society
on behalf of the Bill & Melinda Gates Foundation
17 August 2006
Toronto, Canada



**International
AIDS Society**

Stronger Together

Status of ongoing and planned prep trials

Location	Population	Sponsor	Testing	Results expected	Participants
Botswana	young adults	CDC	TDF/FTC	2008	1,200
Ghana	high-risk women	FHI	TDF	completed 2006	400
Peru/Ecuador	MSM	NIH	TDF/FTC	2009	1,400
Thailand	IDUs	CDC	TDF	2008	2,000
USA	MSM	CDC	TDF	2008	400

Consultation Participants

Betty Akumatey	University of Ghana, Ghana
Edith Clarke	Ministry of Public Health, Ghana
Julie Davids	Community Health AIDS Mobilization Project (CHAMP), USA
Martin Davila	Impacta, Peru
Mary Fanning	National Institutes of Health (NIH), USA
Hugue Fischer	Act-Up Paris, France
Bob Grant	University of California San Francisco/NIH, Peru
Yasmin Halima	International AIDS Society (IAS), Switzerland
Lori Heise	Global Campaign for Microbicides, USA
Tumie Komanyane	Youth Health Organisation, Botswana
Rodney Kort	IAS, Switzerland
Pedro Goicochea	Impacta, Peru
Lynn Paxton	Centres for Disease Control and Prevention (CDC), USA
Leigh Peterson	Family Health International, USA
Renee Ridzon	Bill and Melinda Gates Foundation, USA
Jim Rooney	Gilead, USA
Dawn Smith	CDC, Botswana
Nimit Tienudom	AIDS Access Foundation, Thailand
Emmanuel Trenado	Aides, France
Mitchell Warren	AIDS Vaccine Advocacy Coalition (AVAC), USA

Pre-exposure prophylaxis (PREP) is one of the most promising new HIV prevention interventions now in clinical testing. Results of one clinical trial of PREP showed the intervention to be safe and the data were suggestive, though not conclusive, of some level of protection against HIV infection. Other PREP trials are ongoing and will report safety and efficacy results in the coming years. In August 2006, the International AIDS Society (IAS) convened a meeting of stakeholders in PREP research. The group included trial sponsors, researchers, and community advocates. The purpose of the meeting was to provide stakeholders with an update on PREP research and identify emerging issues related to planned and future PREP trials.

The meeting was also intended to continue a dialogue among stakeholders that began at an IAS consultation on PREP research held in Seattle in May 2005. Those attending the Toronto meeting discussed progress on recommendations from the Seattle consultation, the status of PREP studies, and remaining questions in PREP research and delivery.

Follow up on Seattle recommendations

Renee Ridzon of the Bill & Melinda Gates Foundation and Yasmin Halima of IAS discussed follow through on recommendations made at the Seattle PREP consultation. The major recommendations from that meeting, as noted in the meeting report¹, were to:

- Develop standards of practice for community engagement that can be measured, monitored and adapted for use in different settings
- Strengthen national ethics review boards in order to promote civil society engagement and ensure adherence to national and international ethical guidelines
- Foster community research literacy and capacity through expanded support for these efforts as well as a review of research literacy materials and development of new materials if necessary
- Build true partnerships between researchers in developed and developing countries to ensure investigators in developing countries are not treated as “junior partners”

- Integrate research into other health services so that services provided through PREP clinical studies become part of a country’s comprehensive response to the epidemic
- Promote coordination of PREP research in order to advance this research rapidly and efficiently, and facilitate timely product labeling and distribution if PREP proves safe and effective
- Hold forums on best practices in community engagement at the International AIDS Conference and other international meetings
- Establish a global stakeholders group to move forward with the recommendations made at the meeting and to promote improved communication, coordination, and accountability as part of the PREP research effort
- Follow up on country-specific recommendations with periodic updates on country actions to follow through on recommendations made at the Seattle consultation

While there was progress to report on several of these recommendations it was acknowledged that much work remained. For example, some country groups did not follow through on plans they agreed to at Seattle. Despite efforts by IAS, no global stakeholders group was formed.

Still, there has been strong collaboration between sponsors and donor agencies over the last year. In 2006, IAS convened a meeting on behalf of study sponsors and statisticians to discuss several areas of collaboration, for example developing mechanisms to share safety data across trials. Originally, only the anti-retroviral drug tenofovir (TDF) was being investigated for use as PREP. Based on subsequent animal studies, two antiretroviral drugs – TDF and Truvada (a combination of TDF and emtricitabine) – are now being tested, and Truvada has replaced TDF in some of the trials. This change indicates responsiveness to scientific developments among investigators. Gilead Sciences, the manufacturer of TDF and Truvada, has committed to providing the compounds at a no-profit price of ¢.57 and ¢.87/day (USD) respectively, consistent with the pricing of its Global Access Program, should it be proven efficacious as a prevention technology.

¹ *Building Collaboration to Advance HIV Prevention*, International AIDS Society, September 2005, <http://www.iasociety.org/images/upload/1025.pdf>

Meeting participants shared their own updates on progress since the Seattle consultation. Issues discussed included implementation of community engagement activities, the importance of considering language issues in community meetings on PREP, the sustainability of behavior changes observed among trial participants, and the need for written guidelines regarding community involvement. Investigators were encouraged to “try new things” as they think about community engagement.

Trial updates

Botswana

Investigator Dawn Smith gave an update on the PREP trials that are taking place at two sites in Botswana testing the safety of Truvada (TDF2). The TDF trial will enroll 1200 sexually active volunteers (600 men and 600 women) aged 18 – 29 years. Enrollment where TDF versus placebo was distributed ran from October 2005 through March 2006; 70 individuals were accepted as participants; 61 individuals continue in the study. Researchers are finding a high level of adherence with study visits and study drug. Participants have reported decreased risk behavior since entering the trial, and there is a low rate of sexually transmitted infection (STI) among trial volunteers.

The proposed TDF2 trial was being reviewed by regulatory bodies at the time of the meeting, though community engagement activities had already begun. Eligibility criteria for the trial will include willingness to use hormonal contraception and consent of an adult guardian for those aged 18 – 20. Recruitment will be done through one-to-one contact by recruiters, neighborhood outreach, and a media campaign. Participant support groups have been proposed for all those in the study, and weekly calls to monitor volunteer compliance. Researchers have observed a high baseline rate of osteopenia (thinning of bone mineral density) among participants in the early trial (i.e. before exposure to study medication).

The research team has decided to add questions about reproductive intentions on the semi-annual Audio Computer-Assisted Self-Interviewing (ACASI)

questionnaire. In addition, the research team is planning a community engagement Case Study. An implementation think tank is being established to identify data needed by midlevel public and private sector staff for eventual program planning if PREP is found to be effective.

Ghana

Investigator Edith Clarke next provided an update on the TDF study recently completed in Ghana. The study recruited women at high risk of HIV infection, initially at three sites: Tema, Ghana; Douala, Cameroon; and Ibadan, Nigeria. The study objective was to investigate the safety and effectiveness of a daily oral dose of TDF in prevention of HIV among women at high risk of infection. Enrollment ran from June 2004 through March 2005 (December 2004 in Ghana). The Cameroon and Nigerian sites were later closed.

The safety results from the trial were announced at the conference on the day of the meeting. The study found no evidence that short term use of oral TDF harmed trial participants. Differences in clinical and lab abnormalities between the intervention and placebo groups were not statistically significant. The study also found that there were fewer seroconversions among those receiving TDF, though the number of endpoints was small and the difference is not statistically significant to determine whether TDF was actually protective. There were eight HIV infections among participants: two in the TDF group and six in the placebo group. After the Cameroon study was stopped and participants at that site were no longer given TDF, an additional six participants become infected with HIV, including four that had been randomized to the TDF arm.

There was a relatively high pregnancy rate among participants, even though all participants had said at enrollment that they did not want to get pregnant during the study and they were given condoms to last them until their next study visit. Researchers found that one reason for the high pregnancy rate was that many participants used condoms for casual sex, but not with their regular sexual partners.

Written informed consent for participation was obtained for all those enrolled in the study and participant advocates were available for non-liter-

ate participants. The study had been reviewed by an independent ethical committee. At regular study visits participants received a re-supply of the study pill and were tested for HIV. They were also asked to report any adverse events, and were evaluated for liver and kidney function. All study volunteers were also regularly provided with HIV prevention counseling and given male condoms. Participants were reminded that the intervention is not proven effective and of the importance of maintaining safe sex practices. They were also offered treatment for STIs, and treatment was provided for some conditions, such as malaria, that were unrelated to the study.

Those who seroconverted to HIV during the trial were escorted by a health counselor to support groups for psychological and social support at Tema AIDS Support Association (TASA), a local NGO. Study volunteers who tested HIV positive were also tested for viral load and CD4 as well as for TDF resistance. Study staff made provision for on-going medical care and ARV drugs for participants when needed. For example, in Cameroon and Ghana, contracts were set up with local hospitals to provide ARV services. In Nigeria, seroconverters were connected to the local PEPFAR program.

The research team's partnership with civil society groups was highly beneficial to the trial. The study team did socio-behavioral research before and during the research, and involved community members in that research. There was ongoing contact with a local association of commercial sex workers. In addition TASA was helpful in a variety of ways. This could be attributed to the inclusion of a few of its members in ethics training provided to study staff which gave them a great deal of insight into the ethical principles applied in the research. This in turn led to enhanced co-operation between TASA and the trial team and facilitated the former's rendering of support to participants referred to them from the trial.

Peru

Pedro Goicochea of the Asociacion Civil Impacta Salud y Educacion (Impacta) in Peru made a presentation titled "Assessing Community Needs for Clinical Trials Implementation: Involving Communities in Research Design." He noted that Peru has a high HIV incidence

among gay men and men who have sex with men (MSM) -- between 3.9% and 6.7%. Impacta has a wealth of experience running studies, including HIV treatment, vaccine, and other trials. Extensive consultations were held before the Peru PREP trial was launched. Community Advisory Boards were established or consulted in the cities of Lima, Iquitos, and Pucallpa. Several independent ethics committees reviewed the trial, as did several departments of the Peruvian Ministry of Health.

PREP research has been controversial around the world and Impacta has made a concerted effort to assess community concerns with the trial. In 2005 there were several community consultations on PREP research and formative research was conducted in communities in both 2005 and 2006. This research included 16 focus groups with potential study participants and two focus groups with individuals enrolled in the trial. The concerns raised by community members included:

- Informed consent: whether vulnerable populations would be adequately protected and whether people with low literacy would be able to fully understand the goals and risks of the trial
- Adverse events: whether care would be provided to address any adverse events during the trial, and whether people who seroconverted would receive treatment
- Reimbursement: whether reimbursement for travel and other expenses constitutes coercion to participate
- Behavioral disinhibition: whether trial participants would put themselves at increased risk, either by using condoms less or having more sexual partners, or both

Community members also had a variety of questions about the trial. One person asked, "If I am not HIV positive why will I use an ARV? What is the point? It would be very strange because of the side effects." Another warned that reimbursing participants could be an inducement to sign up for the trial: "Participating is good for your health. When the outreach workers are in the field, they should not talk about money."

The investigator raised his own concern regarding the potential for disruption to trials by external advocates even when best efforts were being made to secure the collaboration and support of local communities.

Those surveyed also identified several potential benefits of the PREP research, including participants knowing they are part of a bigger effort to prevent HIV infection. The trial was perceived as good for the research institutions involved, because it shows the institutions are contributing to the enhancement of a “prevention culture” and the effort to create a healthier community.

Impacta’s involvement in the trial has allowed the organization to provide counseling to more clients, more free health care services, and alternative services aimed at empowering the community. The trial has also repositioned the organization’s efforts on HIV prevention.

Thailand

Lynn Paxton of the CDC gave an update on the TDF trial in Thailand. This trial is enrolling 1,600 injecting drug users (IDUs) aged 20 – 60 years old. The primary study objectives are to determine if TDF prevents HIV infection among IDUs and whether it is safe in this population. Secondary objectives of the study are to evaluate changes in HIV-related risk behaviors and adherence among study participants. Researchers also seek to determine whether TDF is associated with a lower HIV viral load set point or higher CD4 count, or with any antiretroviral resistance in those individuals who do become HIV infected during the trial. The study is cosponsored by the Thai Ministry of Public Health and the CDC. It is being held in the Bangkok metropolitan area.

As of July 2006, 2049 individuals had been screened for the trial and 1162 had been enrolled. The most common reason for failure to enroll at screening was HIV infection; 11% of those who screened out were HIV positive. Eighty enrollees have left the trial since its beginning. The Thai government has waged a severe crackdown on IDUs, and this policy and legal environment presents a challenge for study staff seeking to implement research that is safe for participants and respectful of their rights.

Injection drug use among trial participants appears to be declining during the course of the study. In the first month of the study, over 90% of enrollees reported injecting drugs. One year later, fewer than 70% reported injecting. This decline is similar to a decline in injection drug use observed among Thai IDUs enrolled in a Phase III trial of the vaccine candidate AIDSVAX. Self reports of needle sharing also declined from study month zero to month six, as they did in the vaccine trial.

Trial specific and cross-cutting themes

After the updates on clinical trials, meeting participants were asked to respond to the question, “What are the trial-specific or cross-trial issues that you feel need further discussion?” A variety of issues related to trial participant protections and benefits were raised. One person asked whether participants would be guaranteed access to a product they helped test if it is proven efficacious. Another person asked whether sponsors and researchers would make long term commitments to address any adverse events resulting from the trial. It was also pointed out that it is particularly difficult to run ethical trials in settings where participants may be vulnerable due to significant human rights violations.

There was discussion about how well CABs represent the true interests of actual trial participants, and one person stressed that it is important to make sure actual participants are involved in community consultations. One attendee at the meeting asked how we are supposed to know when the community has been “adequately” involved in trial review and planning. On the issue of risk reduction counseling, one person said it is important to understand which counseling approaches are working well, and then apply those lessons across clinical studies. Another attendee said that trial participants actually receive significant benefits from being in clinical trials and research teams and other stakeholders need to look for new ways to share this information.

Several people at the meeting noted a need for a broader PREP research agenda, including investigation of alternate, or occasional, dosing. Others asked what we may be able to learn about behavioral interventions and behavior change through the PREP trials.

The importance of better communication between communities and researchers was a key topic of discussion. One person said that some sort of mechanism should be established to encourage dialogue among stakeholders. It was suggested that the existing AVAC website is a good venue for such a discussion. The URL is www.prepwatch.org. There was also interest in expanding the involvement of community members and researchers at the US trials sites in the emerging global discussion on PREP.

Other ideas included having staff members and community representatives from one trial site go to other sites to exchange information and experiences. There is a need for dissemination of information that communities can readily understand and use, including information that is in languages other than English and is accessible to non-scientists. Some information should come from community members and NGOs – scientists should not be the sole source of information on PREP research.

Bill & Melinda Gates Foundation and Rodney Kort from the International AIDS Society noting that their organizations were committed to facilitating ongoing dialogue regarding PREP research and its potential implementation as a promising new prevention technology.

Issues for future PREP research

The session concluded with a discussion about future questions in PREP research. One person said it will be important to know which drug being tested - TDF or Truvada - is most effective. Researchers need to be planning now for testing of other products if neither of the ARVs currently under study prove safe and effective. Several meeting participants said that even if research does determine one or more drugs are effective as PREP, additional studies will be necessary to understand the safety of PREP for pregnant women and adolescents, and among discordant couples.

Another set of questions concerns the affect of PREP research results on the overall prevention effort. When PREP studies report findings, how will this data influence public health planning and future PREP and other prevention research trials? More attention is needed to planning communications around delivery of PREP, including clear communications about partial efficacy. Finally, it will be essential to carefully consider which populations need PREP the most, and what supports are needed to help them access and use the product appropriately. The consultation ended with both Renee Ridzou from the

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